Shake-up in AI drug discovery

AstraZeneca has teamed with artificial intelligence (AI) machine learning firm BenevolentAI to discover new targets for drugs to treat chronic kidney disease and idiopathic pulmonary fibrosis. The news came on 30 April, shortly after *STAT* reported that IBM would stop selling its machine learning AI tool Watson for Drug Discovery (*Nat. Biotechnol.* **33**, 10–11, 2015), owing to poor financial performance. These opposing fates reflect the controversy that runs in the field over how useful AI-powered efforts may be for target discovery. GlaxoSmithKline was an early entrant into AI when, in 2013, it teamed up with IBM, and by 2017 many collaborations to use AI-based drug discovery followed. Most platforms use natural language systems trained in the life sciences to sift big data sets, which include 'omics' information on genes, RNA, proteins and metabolites as well as chemical databases and clinical data, to find new associations and patterns with which to generate new hypotheses. BenevolentAI's platform in April released results from a study initiated a year earlier with Action Against AMD, which identified seven existing drugs that could be repurposed for acute macular degeneration. In March 2019, Exscientia, a Dundee, UK-based university spinout, announced a collaboration with Celgene to discover small molecule drug candidates in oncology and autoimmunity. Despite pharma's buy-in, critics contend that AI has yet to accelerate drug discovery as promised, a view underlined by IBM's limited success in drug discovery. For now, AI is blazing a trail in imaging diagnostics, with AI-based diagnostics for stroke, wrist fractures and diabetic retinopathy approved by the US Food and Drug Administration.

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"This is an example where the FDA, for a long period of time, took enforcement discretion, then the field grew. Then it becomes hard to step in and actually apply the regulation. There are literally hundreds of clinics, and some of them are engaging in very risky actions. They're crossing the line." Former FDA commissioner Scott Gottlieb notes that the agency's relaxed attitude may have encouraged rogue stem cell clinics to multiply. (*ProPublica*, 7 May 2019)

Drug makers chase anti-flu pill

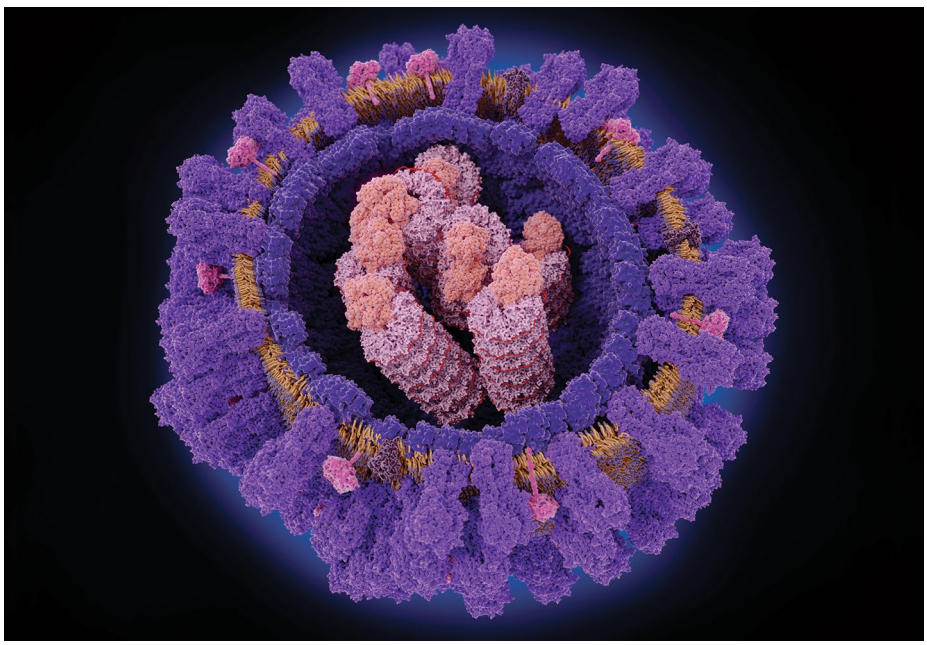
Drug makers are targeting flu virus vulnerabilities to develop antivirals that not only stop infections in their tracks, but also temper emergence of drug resistance.

Researchers from Janssen and Scripps have uncovered a small molecule that neutralizes influenza A group 1 viruses, the most common flu strains. Writing in *Science* (**363**, eaar6221, 2019), the team describes how they studied broadly neutralizing anti-hemagglutinin (HA) antibodies obtained from individuals protected by vaccination and used a large chemical library to identify small molecules with the same protective action as virus-blocking antibodies. A few anti-HA monoclonal antibodies are already in clinical development as passive immunotherapies to treat critical cases and the infections in the elderly in the event of an influenza pandemic. But drug makers continue to chase an antiviral pill that would work across different flu types and mitigate viral resistance, as well as being decidedly more practical.

The biggest-selling orally active agent against flu, Tamiflu (oseltamivir), arrived 20 years ago, closely followed by Relenza (zanamivir), an inhaled powder. These drugs target and block neuraminidase, an influenza virus surface protein, to prevent the release of new virus particles from infected cells. But clinical data have shown that mutations in the neuraminidase gene rapidly emerge that reduce the agents' efficacy, resulting in drug-resistant influenza strains.

Last year, Roche and Shionogi launched another class of oral antiviral medicine, Xofluza (baloxavir marboxil), that stops viral replication by blocking influenza-specific RNA polymerase. Xofluza is active against both influenza A and B viruses, including flu strains resistant to Tamiflu.

The new work focuses on yet another class of small-molecule agent that targets the conserved portion of the HA stem. Viral HA is a glycoprotein that is integral to influenza virus infectivity. HA has two key roles in viral infection: first, the HA head binds to the sialic acid on the surface of upper respiratory tract cells to gain entry. Once internalized, it forms a new membrane-encapsulated compartment, or endosome, within these cells. Following that, the endosome membranes fuse with the virus particle's own membrane in a process driven by the HA stem, which results in the release of viral RNA particles into the cell's cytoplasm and their subsequent replication. Investigators hope to use small molecules to target the conserved HA stem region



The influenza virus, with its RNA core (lavender, peach) surrounded by a lipid bilayer (gold) spiked with hemagglutinin (violet) and neuraminidase (rose). Credit: Juan Gaertner/Science Photo Library